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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,666	08/12/2004	Patrick Stordeur	DECLE35.002APC	9946

20995 7590 11/01/2007

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ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
11/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/501,666	STORDEUR ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,9,11,12,18,20-23,25-36 and 40-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,9,11,12,18,20-23,25-36 and 40-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's amendment submitted 8/13/2007 is acknowledged. Claims 1-4, 6, 7, 9, 11, 12, 18, 20-23, 25-36, and new claims 40-66 are pending in the application.

The objection to claims 32-36 made in OA 2/14/2007 is withdrawn in view of Applicant's amendment.

The rejection of claims 5, 8, 10 and 13 under 35 U.S.C. 112, 2nd paragraph is withdrawn in view of the cancellation of these claims.

The rejection of claims 1-4, 6 and 7 under 35 U.S.C. 102(b) over Hamel et al (Journal of Clinical Microbiology, Feb 1995, Vol 33, No 2, pp 287-91) is maintained for the reasons of record and reiterated below. The rejection of claim 12 is withdrawn, since Hamel does not teach a sample that is both whole blood *and* 100 µl as recited in the amended claim. The rejection of claims 20, 21 and 22 is withdrawn, since Hamel monitors changes in levels of nucleic acids in tissue culture samples, not samples of whole blood.

The rejection of claims 9 and 11 under 35 U.S.C. 103 over Hamel et al in view of Winer et al (Analytical Biochemistry 270, 41-49, 1999) is maintained for the reasons of record and reiterated below.

The rejection of claim 18 under 35 U.S.C. 103 over Hamel et al in view of Walker (J. Biochem Molecular Toxicology, 15(3):121-127, 2001) is maintained for the reasons of record and reiterated below.

The rejection of claims 23 and 26-31 under 35 U.S.C. 103 over Hamel et al in view of Kammula et al (J. Natl Cancer Inst 92:1336-44, 2000) is maintained and extended to claims 20, 21 and new claims 40-65 for the reasons of record and reiterated below. The rejection of claim 25 is withdrawn, since this claim has been amended to depend only from claim 22, which requires monitoring changes in levels of nucleic acid in whole blood for the purpose of diagnosis.

Applicant's arguments are addressed following each rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamel et al (JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1995, Vol. 33, No. 2, p. 287–291, prior art of record).

With regard to claim 1, Hamel teaches a method for the quantification of real *in vivo* levels of low-level or unstable RNA from whole blood comprising the steps of:

(a) collecting the whole blood in a tube comprising a compound inhibiting RNA degradation and/or gene induction (See page 288, column 1, "RNA extraction": "Two drops of blood containing sodium citrate or heparin or four drops of serum, other fluids, or swab suspensions were vortex mixed with 0.5 ml of Cat-14 containing 1 drop of yeast RNA." Cat-14 is tetradecyltrimethyl-ammonium oxalate (see page 287, last paragraph

preceding "Materials and Methods"), which according to claim 4, must be *a compound which inhibits RNA degradation and/or gene induction.* One of ordinary skill in the art would have reasonably inferred this was done in some sort of "tube", since the samples were vortexed, centrifuged and inverted to drain off the supernatant (see page 288, column 1, "RNA extraction"),

(b) forming a precipitate comprising nucleic acids (See page 288, column 1, "RNA extraction": "For all types of specimens, after the addition of Cat-14 and yeast RNA, samples were immediately vortex mixed for about 30 s and were left at room temperature for 10 to 30 min." This evidently forms a precipitate, as evidenced by the text cited for the next limitation.),

(c) separating said precipitate of step (b) from the supernatant (See page 288, column 1, "RNA extraction": "Samples were then microcentrifuged for 5 min, drained by inverting them, and briefly microcentrifuged (5 s). Any remaining supernatant was removed with filter barrier micropipet tips..."),

(d) dissolving said precipitate of step (c) using a buffer, forming a suspension (See page 288, column 1, "RNA extraction": "...and the pellets (containing precipitated Cat-14 salt of RNA and DNA) were dissolved in 0.2 ml of GITC buffer (4 M guanidine thiocyanate, 0.2 M sodium acetate [pH 4.0], 0.1 M 2-mercaptoethanol), vortex mixed (intermittently for up to 5 min), and then kept on ice."),

(e) isolating nucleic acids from said suspension of step (d) using an automated device (See page 288, column 1, "RNA extraction": "For each extraction, samples were

vortex mixed for 30 s and microcentrifuged for 5 min at 48C." Vortex mixers and microcentrifuges are *automated devices*.),

(f) dispersing/distributing a reagent mix for RT-PCR using an automated device (See page 288, column 2, "RT-PCR": "In order to minimize pipetting errors..." and "...only filter barrier micropipette tips were used...". This implicitly teaches micropipettes, which are *automated devices*.),

(g) dispersing/distributing the nucleic acids isolated in step (e) within the dispersed reagent mix of step (f) using an automated device (See page 288, column 2, "RT-PCR": "In order to minimize pipetting errors..." and "...only filter barrier micropipette tips were used...". This implicitly teaches micropipettes, which are *automated devices*.), and,

(h) determining the real in vivo levels of low-level or unstable RNA using the nucleic acid/RT-PCR reagent mix of step (g) in an automated setup (See page 288, column 2, "RT-PCR": "RT-PCR was performed on a programmable thermocycler." A programmable thermocycler is an *automated setup*, which *uses the nucleic acid/RT-PCR reagent mix*.).

With regard to claim 2, see page 288, column 1, "RNA extraction": "For all types of specimens, after the addition of Cat-14 and yeast RNA, samples were immediately vortex mixed for about 30 s and were left at room temperature for 10 to 30 min." This evidently forms a precipitate, as evidenced by the text cited for limitation (c) of claim 1. Therefore, collection of the sample in a tube with the compound and the formation of a precipitate occurred *simultaneously*.

With regard to claim 3, Cat-14 is tetradecyltrimethyl-ammonium oxalate (see page 287, last paragraph preceding "Materials and Methods"), which according to claim 4, must be a *quaternary amine surfactant*.

With regard to claim 4, Cat-14 is *tetradecyltrimethyl-ammonium oxalate* (see page 287, last paragraph preceding "Materials and Methods").

With regard to claim 6, it has already been stated in the discussion of claim 1 above that one of ordinary skill in the art would have reasonably inferred that the samples were manipulated in tubes, since the samples were vortexed, centrifuged and inverted to drain off the supernatant (see page 288, column 1, "RNA extraction"). The term "tube" and "blood collection tube" are not explicitly defined in the specification, and thus the term "blood collection tube" does not structurally distinguish over the "tube" implicitly taught by Hamel. Regarding the tube being "*open*" or "*closed*", the tubes implicitly taught by Hamel had to have been either open or closed, or intermittently opened and closed; there is no other logical possibility.

With regard to claim 7, Hamel teaches *guanidine-thiocyanate-containing buffer* (see page 288, column 1, "RNA extraction": "...and the pellets (containing precipitated Cat-14 salt of RNA and DNA) were dissolved in 0.2 ml of GITC buffer (4 M guanidine thiocyanate, 0.2 M sodium acetate [pH 4.0], 0.1 M 2-mercaptoethanol), vortex mixed (intermittently for up to 5 min), and then kept on ice.").

Response to Arguments

Applicant's arguments filed 8/13/2007 have been fully considered but they are not persuasive. As a preliminary matter, Applicant has raised arguments as to both why

Hamel does not anticipate the claims, and as to why the claims are not obvious over Hamel. Only the former arguments will be addressed here, since arguments as to obviousness are irrelevant (these arguments will be addressed with regard to the rejections under 35 U.S.C. 103 presented below).

Applicant first argues (item 1, bottom of page 15 of the response) that no quantification has been performed in Hamel's method. This argument is not persuasive. The claims only require "determining the real *in vivo* levels..." (e.g. claim 1, step (h)). The claim does not recite any particular steps involved in such "determining", nor does the specification define "determining" in such a way as to distinguish over Hamel. Figure 1 of Hamel shows an analysis of BVDV viral nucleic acid from "various clinical specimens" alongside a set of serial dilutions of cell culture supernatant comprising known amounts of the virus (100, 10, 1 and 0.1 $TCID_{50}$; see last paragraph, page 288 and figure 1 and caption). This constitutes a "determination" of the levels of the viral nucleic acids in the clinical samples, since the intensities of the bands from the clinical samples are visualized along with those of the known amounts of viral nucleic acids in the diluted culture supernatants in figure 1.

Applicant then argues (item 2, top of page 16) that RNA from bovine viral diarrhea virus does not constitute "low level or unstable RNA". This argument is not persuasive. The new limitation "levels of low-level or unstable" as applied to RNA (claim 1), DNA (claim 18), CTLs (claim 28) or particular transcripts (claims 28-31), or any other nucleic acid does not distinguish over Hamel. There are no definitions for "low-level" or "unstable" in the original disclosure, and therefore these terms do not

define any particular concentration or half-life required to in order to be considered "low-level" or "unstable". Furthermore, Applicant's argument that "RNA from viruses are present at high levels" is countered by Hamel's teaching: "[s]pecimens were not analyzed by EM, because conclusive identification by EM is difficult because of the inconsistency in the morphology of BVDV and because of the low concentrations of virus in specimens" (page 289, column 2, paragraph 2).

Applicant further argues (item 3, page 16) that the vortex mixers, microcentrifuges, micropipettes and thermocycler used in Hamel's method "should be seen as different and clearly distinct from the automated setup disclosed in the present application." Applicant points out several devices disclosed in the specification (MagNA Pure LC Instrument, AutoGenprep 960, etc) and states: "[t]he automated devices referred at in the present claims are thus clearly different from the devices used by Hamel et al." In response to applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which applicant relies (i.e., MagNA Pure LC Instrument, AutoGenprep 960, etc) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims only require the use of automated devices, and the specification does not define an "automated device" in such a way as to preclude the vortex mixers, microcentrifuges, micropipettes and thermocycler used in Hamel's method as being considered "automated devices".

Furthermore, Applicant is cautioned that, should the claims be amended to recite particular automated devices disclosed in the specification, a rejection under 35 U.S.C. 112, 2nd paragraph may be imposed. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. Applicant may, however, import structural limitations describing these devices, assuming there is adequate written descriptive support under 35 U.S.C. 112, 1st paragraph.

Therefore, Hamel does teach all of the limitations of the presently claimed invention and the rejection under 35 U.S.C. 102(b) is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamel et al (JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1995, Vol. 33, No. 2, p. 287–291) in view of Winer et al (Analytical Biochemistry 270, 41–49 (1999)).

Hamel teaches the method of claim 1 as discussed above in the rejections under 35 U.S.C. 102. Hamel does not teach RNA capturing beads or real time PCR.

With regard to claim 9, Winer teaches isolation of nucleic acids using RNA-capturing beads (see page 42, column 1, "mRNA Preparation").

With regard to claim 11, Winer teaches determination of in vivo levels of RNA using real time PCR (see page 41, column 2, first sentence of second paragraph for example: "In this article, we validate the use of this real-time RT–PCR method to analyze gene expression...").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the method of claim 1 as taught by Hamel, incorporating the use of oligo(dT) beads for capturing the mRNA, which Winer teaches "minimized DNA contamination" (see Winer abstract). It would also have been obvious to practice Hamel's method using real time PCR (as taught by

Winer) because real time PCR represented an improvement over the base method of PCR, and it would have thus been obvious to apply this improvement to any PCR application.

Claims 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hamel et al (JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1995, Vol. 33, No. 2, p. 287–291) in view of Walker (J BIOCHEM MOLECULAR TOXICOLOGY, Volume 15, Number 3, 2001).

With regard to claim 18, Hamel teaches the method of claim 1 as discussed above in the rejections under 35 U.S.C. 102, but does not teach skipping the RT reaction or quantifying DNA.

Walker teaches quantifying DNA by PCR (see entire document, for example, section entitled "RTAQ-PCR METHODOLOGY", beginning on page 121).

It would have been *prima facie* obvious to use Hamel's method to quantify DNA as well as RNA. It would have been obvious because Hamel teaches that Catrimox-14 precipitates DNA as well as RNA (see page 288, column 1, "RNA extraction": "Any remaining supernatant was removed with filter barrier micropipet tips, and the pellets (containing precipitated Cat-14 salt of RNA and DNA) were dissolved in 0.2 ml of GITC buffer)"), and because Walker points out clear motivations for quantifying DNA (for example, page 124, column 2, "DNA Analysis: Molecular Genetics" and "Exposure Monitoring").

Claims 20, 21, 23, 26-31 and 40-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamel et al (JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1995, Vol. 33, No. 2, p. 287–291) in view of Kammula et al (J Natl Cancer Inst 2000;92:1336–44). The inclusion in this rejection of claims 20, 21 and 40-65 is new and necessitated by Applicant's amendment.

Hamel teaches the method of claim 1 as discussed in the rejection under 35 U.S.C. 102 above. It is noted that Hamel shows his method to work with whole blood samples.

Hamel does not apply his method monitoring changes in nucleic acid levels in whole blood samples, as recited in claims 20 and 21. In addition, Hamel does not apply this method for the purpose of monitoring changes in nucleic acids for the production of a medicament for curing a disease (claims 23), or more particularly a compound recited in claim 26, or more particularly an immuno-related disease (claims 40, 41), or more particularly a transcript recited in claims 42-45. Hamel also does not apply his method to detecting or monitoring epitope specific CTLs (claims 27, 28) or immuno-related transcripts (claims 27, 29) for the purpose of identifying an agent capable of modifying the immunological status of a subject (claims 28, 29) or for diagnosis/prognosis/monitoring of a clinical status affecting the immune system in a subject (claims 30, 31), wherein the immunological status is selected from those recited in claims 46, 51, 56 and 61, wherein the immuno-related transcripts were selected from those recited in claims 47-50, 52-55, 57-60 and 62-65.

With regard to claims 20, 21 and 23, Kammula teaches *a method for the monitoring/detection of changes of in vivo nucleic acids of a biological agent* (PBMCs) *in a biological sample* (see page 1337, column 1, 3rd paragraph: "In this study, we have used a sensitive, quantitative, real-time polymerase chain reaction (PCR) assay to directly assess the immune status of PBMCs from patients prior to any in vitro stimulation with antigen"; i.e. *in vivo* changes of nucleic acids), *in order to screen for a compound for the production of a medicament for curing a disease* (see page 1337, column 1, 2nd paragraph: "...treating patients with metastatic melanoma with a synthetically modified melanoma peptide..." and see page 1339, last paragraph in column 1 continuing in column 2, especially text cited for claim 27 below). Kammula was screening a potential vaccine for "curing" melanoma.

With regard to claim 26, Kammula teaches a vaccine (which is also a peptide) (see page 1339, last paragraph in column 1 continuing in column 2, especially text as cited for claim 27 below).

With regard to claims 40 and 41 melanoma is cancer, which is an "immuno-related disease".

With regard to claims 42-45, Kammula teaches IL-2 and IFN-γ, which are at least cytokines, GM-CSF, which is at least a growth factor, and CD8, which is at least a T cell receptor (see figure 1 and page 1338, column 2, "Measurement of mRNA levels of other cytokines").

With regard to claim 27, Kammula teaches *a method for the detection/monitoring of epitope specific CTLs* **and** *immuno-related transcripts* (see page 1339, last paragraph in column 1 continuing in column 2):

> "To develop an assay that directly detects specific antigen recognition and reactivity by CTLs in peripheral blood, we obtained PBMCs from a patient before and after two rounds of g209-2M vaccination... As shown in Fig. 1, c, preimmunization PBMCs demonstrated no detectable changes in IFN γ mRNA (after normalization to CD8 mRNA) after g209 peptide exposure. However, postimmunization PBMCs showed a marked increase in IFN γ mRNA, with peak expression between 2 and 3 hours after peptide exposure. In addition, we noted that the g209 peptide induced gene expression for the CD69 representing a marker of CTL activation, the IL-2α receptor (CD25), and the cytokines tumor necrosis factor-α, GM-CSF, and IL-2. Control peptides resulted in no change in cytokine mRNA expression in either the preimmunized or postimmunized samples (data not shown)." (citations omitted)

The fact that control peptides resulted in no change in cytokine mRNA expression demonstrates that, in addition to detecting immuno-related transcripts, Kammula was monitoring epitope specific CTLs.

With regard to claim 28, Kammula teaches *a method to identify an agent capable of modifying the immunological status of a subject via the analysis of epitope specific CTLs comprising the steps of:*

(a) applying an immunomodulatory agent(s) into a subject (see page 1339, last paragraph in column 1 continuing in column 2: "To develop an assay that directly detects specific antigen recognition and reactivity by CTLs in peripheral blood, we obtained PBMCs from a patient before and after two rounds of g209-2M vaccination."),

(b) sampling whole blood from said subject (see page 1339, last paragraph in column 1 continuing in column 2: "To develop an assay that directly detects specific antigen recognition and reactivity by CTLs in peripheral blood, we obtained PBMCs from a patient before and after two rounds of g209-2M vaccination." Note PBMC stands

for peripheral blood mononuclear cells. Although Kammula separates out the PBMCs from whole blood, he nevertheless necessarily sampled whole blood from his subjects.),

(c) optionally, pulsing blood cells present in the whole blood sample of step (b) with an identical/similar and/or different immunomodulatory agent as applied in step (a) (see page 1338, column 1, "In Vitro Sensitization Assay of Peptide and Melanoma-Specific CTL Reactivity": "The harvested cells were then stimulated with melanoma cells or the antigen-processing-defective, HLA-A*0201-expressing T2 cells pulsed with 1 μM g209 peptide or a control peptide g154 for 18–24 hours at 37 °C." (citations omitted)),

(k) detecting/monitoring/analyzing the in vivo levels of epitope specific CTLs-related transcripts in the dispersed solution of step (j) in an automated setup (see page 1338, column 1, "Quantitative Real-Time PCR": "Gene expression was measured with the use of the ABI Prism 7700 Sequence Detection System"; this is an automated setup),

(l) identifying agents able to modify the immunological status of said subject, whereby, in case the agent of step (a) is already present in the subject, step (a) is omitted (see page 1339, column 2:

> "However, postimmunization PBMCs showed a marked increase in IFN γ mRNA, with peak expression between 2 and 3 hours after peptide exposure. In addition, we noted that the g209 peptide induced gene expression for the CD69 representing a marker of CTL activation, the IL-2α receptor (CD25), and the cytokines tumor necrosis factor-α, GM-CSF, and IL-2. Control peptides resulted in no change in cytokine mRNA expression in either the preimmunized or postimmunized samples (data not shown)." (citations omitted)

thus, Kammula identified the g209 vaccine as an agent able to modify the immunological status of a subject).

With regard to claim 29, the only difference between this claim and claim 28 is the more general detection of immuno-related transcripts, rather than the more specific detection of epitope specific CTLs-related transcripts (compare step (k) of each claim). In any event, Kammula teaches *detecting/monitoring/analyzing the in vivo levels of immuno-related transcripts* (see discussion of step (k) for claim 28).

With regard to claim 30, Kammula teaches *monitoring of a clinical status affecting the immune system in a subject comprising the steps of (a) sampling whole blood from said subject*, as discussed for claim 28 above.

With regard to claim 31, Kammula teaches *monitoring of a clinical status affecting the immune system in a subject comprising the steps of (a) sampling whole blood from said subject* and *(b) pulsing blood cells present in the whole blood sample with an identical/similar and/or different immunomodulatory agent as present in the subject* as discussed for claim 28 above.

With regard to claims 46, 51, 56 and 61, Kammula teaches cancer.

With regard to claims 47-50, 52-55, 57-60 and 62-65, Kammula teaches IL-2 and IFN-γ, which are at least cytokines, GM-CSF, which is at least a growth factor, and CD8, which is at least a T cell receptor (see figure 1 and page 1338, column 2, "Measurement of mRNA levels of other cytokines").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the method of Hamel to isolate the mRNA in the method of Kammula. The combination merely represents the application of a known method for isolating nucleic acids and determining their levels

(as taught by Hamel) for the known purposes of monitoring changes in levels of particular transcripts in a subject in order to monitor the immunological status of that subject, as well as identifying curative and immunomodulatory agents, as taught by Kammula. In other words, it would have been obvious to substitute the nucleic acid isolation/amplification protocol taught by Hamel for the protocol used by Kammula when practicing Kammula's method, because both were known protocols for the same purpose.

Response to Arguments

Applicant's arguments filed 8/13/2007 have been fully considered but they are not persuasive. Applicant's arguments (page 21 of the response) rely solely on the arguments presented against the Hamel reference (pages 15-21 of the response). Applicant's arguments that Hamel does not anticipate the method of claim 1 have already been addressed. The remainder of Applicant's argument begins at the penultimate paragraph of page 16.

Applicant argues "Hamel et al. do not suggest or lead the skilled person to the concept of the present invention". It is unclear whether Applicant is asserting that Hamel does not suggest the combination of his method with the teachings of Winer (which is doubtful, since the statement is made in arguing the 35 U.S.C. 102(b) rejection), or whether Hamel does not suggest applying his method to "real in vivo levels of low-level or unstable RNA from whole blood", or whether Hamel does not suggest applying his method in a "more automated method". With regard to the first possibility (motivation to combine the teachings of Hamel and Winer), this argument is not

persuasive, because a clear rationale as to why the skilled artisan would have combined the teachings of Hamel and Winer was discussed in the rejection. With regard to the latter two points, as discussed in response to Applicant's argument over the 35 U.S.C. 102(b) rejection, the terms "low-level", "unstable" and "automated device" are not defined in such a way as to distinguish over Hamel. Also, Hamel teaches "[s]pecimens were not analyzed by EM, because conclusive identification by EM is difficult because of the inconsistency in the morphology of BVDV and because of the low concentrations of virus in specimens" (page 289, column 2, paragraph 2). Thus, the viral nucleic acids analyzed by Hamel certainly qualify as "low-level". Additionally, there is nothing in the claims that preclude the vortex mixers, microcentrifuges, micropipettes and thermocycler used in Hamel's method as being considered "automated devices". Finally, Hamel specifically states: "[o]ur assay was performed with the minimum amount of manual pipetting required for surveying large numbers of specimens and, with minor modifications, might be suitable for automated robotic workstations" (page 291, column 1, paragraph 2). Thus, even if the devices used by Hamel were not "automated devices", which the examiner does not concede, Hamel explicitly suggests applying his method in a "more automated method".

Applicant argues at the bottom of page 16 that the "claimed method allows the quantification of low copy or unstable RNA present in a cell at the moment of sampling in an extremely accurate way". Thus the claims have been amended to recite that "real in vivo levels" are analyzed. This argument is not persuasive. First, Hamel teaches all the steps recited in the method of claim 1. Therefore, if there is something missing from

Hamel's disclosure that is required to achieve "an extremely accurate" result, it is also missing from the claims (which would constitute grounds for a rejection under 35 U.S.C. 112; see MPEP 2172.01). Second, the amendments to the claims to include the word "real" (describing *in vivo* levels of low-level or unstable RNA or various transcripts) do not distinguish the claimed invention over the prior art. Paragraph [0007] of the published instant application reads:

"With `real in vivo levels` is meant the level(s) of transcript(s) present in the biological agent at the time of the sampling."

Thus, the term "real" derives it's meaning from the fact that the sample is "collected in a tube comprising a compound inhibiting RNA degradation and/or gene induction" (see step (a) of claim 1). Since Hamel's method involves collecting the sample in a tube comprising the very same compound as claimed in claim 3 (see rejection of claim 3 above), Hamel's method meets the limitation relating to "real *in vivo* levels".

Applicant's arguments on page 17 describing the problem to be solved and the purported solution, as well as citation from MPEP 2145, are unavailing, because there are no differences between the method *as claimed* and the method taught by Hamel. Applicant states (bridging pages 17-18) that the prior art (the examiner will assume Applicant is referring to Hamel's disclosure) is not a "walk away system". This term does not appear in the claims and furthermore is not defined in such a way as to distinguish over Hamel. Vortexers, centrifuges, and thermocyclers may all be "walked away from" during operation. Furthermore, Hamel explicitly states: "[o]ur assay was

performed with the minimum amount of manual pipetting required for surveying large numbers of specimens and, with minor modifications, might be suitable for automated robotic workstations" (page 291, column 1, paragraph 2). Therefore, Applicant's assertion that "a skilled person would never automate one of said existing methods in order to accurately quantify low copy or unstable RNA", and enumerated arguments to this effect (page 18), are not persuasive.

Likewise Applicant's remark that a skilled person would never use small volumes when there is a need to quantify low levels of RNA (top of page 19) is not persuasive. Hamel is one of skill in the art. Hamel uses two drops of whole blood (page 288, column 1, "RNA extraction"), which is a small volume. Hamel determines levels of BVDV nucleic acid, and teaches that this virus occurs at "low concentrations [] in specimens" (page 289, column 2, paragraph 2).

Applicant's remarks that blood samples are "very precious samples" and that, therefore, one of skill would "never play with conditions to find a more optimal method, in particular when not expecting a high chance of success" is simply inconsistent with history and standard practice. The very existence of the *in vitro* diagnostics market is evidence that one of skill in the art would clearly use whole blood samples to find more optimal methods (existing whole blood *in vitro* diagnostic assays would never have been approved by the FDA without first testing such assays). Furthermore, this argument appears to be based on a difference between Hamel's method and the claimed methods. Thus this argument is not persuasive, because the only difference between the disclosure of Hamel and the claims under discussion is the *application* of the basic

method of Hamel (i.e. there is no difference between the basic method steps taught by Hamel and the instant methods *as claimed*).

Applicant's argument that at the time of filing of the instant application that Catrimox14 had "completely disappeared from the market, making it nearly impossible to further work on the method disclosed" (page 19) is irrelevant. Hamel's disclosure occurred prior to the filing of the instant application, his method is not different from the method steps *as claimed*, and the reagent was available to him. Furthermore, Applicant's argument that a particular material required for the claimed invention was not available at the time of filing to the application is inconsistent with the requirements of 35 U.S.C. 112, 1st paragraph, since Applicant's disclosure does not teach how to synthesize Catrimox14 (aka tetradecyltrimethyl-ammonioum oxalate recited in claim 4). As discussed in MPEP 2164.01(b):

"The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981)."

For these reasons, the Applicant's remaining arguments on page 19 are not persuasive.

Applicant argues as though there were some limitation of the basic method of claim 1 which is not taught by Hamel. As discussed at length above, there is no such

limitation. The only difference is in how the basic method (sample collection, nucleic acid extraction, RT-PCR) is *applied* (e.g. to monitor *changes* in nucleic acid levels, to assay for *specific transcripts*, etc). This difference in *application* is the reason why the rejection of the claims fall under 35 U.S.C. 103, requiring the secondary references relied upon. Applicant has presented no arguments as to the obviousness or non-obviousness of applying Hamel's basic method to the applications/specific transcripts taught in the secondary references, but has instead argued a difference in basic methodology. While there may be elements in the instant specification that distinguish over Hamel, these elements are not found in the *claims*. Therefore, Applicant's argument presented at page 19, penultimate paragraph (no reasonable expectation of success: "[h]e will thus not try to explore experimental conditions from which no results may be expected") is premature. Likewise, the statement in the following paragraph, which seems to allege skepticism of experts ("many scientists were surprised"), is also premature. Applicant's arguments at paragraph 2, page 20 through paragraph 3, page 21, which touts the accuracy and sensitivity of Applicant's methods, are similarly unavailing. Hamel teaches all of the steps of the method of claim 1. If Applicant wishes to argue unexpected results, Applicant must first incorporate a limitation that distinguishes over the method of Hamel, and then show that such a limitation achieves unexpected results.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 41, 46, 51, 56 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 32, 41, 46, 51, 56 and 61, the phrase "e.g" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 42, 47, 52, 57 and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant has not enabled one of ordinary skill in the art to practice the claimed methods with markers “to be discovered”. It would require undue experimentation to discover such markers in the first place.

Claim Rejections - 35 USC § 103

Claims 12 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamel et al (JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1995, Vol. 33, No.

2, p. 287–291). This is a **new rejection** necessitated by Applicant's amendment to claim 1 and addition of new claim 66, requiring the sample be "whole blood".

Hamel teaches using a biological sample of 100 μl (see page 288, column 2, "RT-PCR detection limit": "Total RNA was extracted, with and without added carrier yeast RNA, from duplicate 100 μl aliquots of several viral dilutions...").

Hamel does not teach a sample that was both whole blood *and* the particular volumes recited in the claims. However, Hamel does apply the general steps of sample collection, nucleic acid extraction and RT-PCR to whole blood samples (see page 288, column 1, "RNA extraction": "Two drops of blood containing sodium citrate or heparin or four drops of serum, other fluids, or swab suspensions were vortex mixed with 0.5 ml of Cat-14 containing 1 drop of yeast RNA").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to apply the methods taught by Hamel to whole blood samples of 100 μl (note that the "two drops of blood" taught by Hamel would have been fairly close to 100 μl in volume). Hamel had already shown that whole blood could be analyzed by the method, and so provided more than a reasonable expectation of success. The minor difference between "two drops" and 100 μl of whole blood is not a patentable distinction. If anything, this amounts to a minor change in scale, of which MPEP 2144.04(IV)(A) notes, quoting from *In re Rinehart*: "mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled." *In re*

Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (531 F.2d at 1053, 189 USPQ at 148).

Claims 20-22, 25, and 32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamel et al (JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1995, Vol. 33, No. 2, p. 287–291) in view of Heller et al (Proc. Natl. Acad. Sci. USA Vol. 94, pp. 2150-2155, March 1997) and Linsley et al (USPN 6,271,002). This is a **new rejection** necessitated by Applicant's amendment to claim 1 (requiring the sample be "whole blood"), claim 25 (to limit dependency to claim 22), and claims 32-36 (correcting improper multiple dependency).

Hamel teaches the method of claim 1 as discussed in the rejection under 35 U.S.C. 102 above. It is noted that Hamel shows his method to work with whole blood samples.

Hamel does not apply his method monitoring changes in nucleic acid levels in whole blood samples, as recited in claims 20 and 21. In addition, Hamel does not apply this method for the purpose of monitoring changes in nucleic acids for the diagnosis of a disease (claim 22), an immuno-related disease (claim 25), a disease recited in claim 32, or the transcripts recited in claims 33-36.

With regard to claims 20-22, 25 and 32-36 Heller teaches measuring differential gene expression (i.e. changes in gene expression) for a number of genes (see figure 1; page 2153 "Expression profiles in primary chondrocytes and synoviocytes of human RA tissue", continuing on page 2154) for the diseases rheumatoid arthritis and irritable

bowel syndrome (page 2150, paragraph preceding "Methods"). The diseases and genes taught by Heller meet the limitations of claims 25 and 32-36.

Heller does not teach diagnosing.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to apply the protocol taught by Hamel for isolating RNA, RT-PCR, and determination of levels of nucleic acid for the purpose of monitoring changes in the genes taught by Heller for the purpose of diagnosing the diseases for which Heller demonstrates gene expression profiles. It was known in the art to use gene expression profiles characteristic of a disease to diagnose that disease, as described, for example, by Linsley at column 21, lines 3-6:

"Gene expression profiling can be done for purposes of screening, diagnosis, staging a disease, and monitoring response to therapy, as well as for identifying genetic targets of drugs and of pathogens."

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

scw

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